M345 N.pdf

10/23/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Resea
1401 Rockville Pike
Rockville MD 20852-1448

OCT 10 1997

Certified-Return Receipt Requested

WARNING LETTER

Charles B. Hanna, M. D.
Spartanburg Medical Center
101 East Wood Street
Spartanburg, South Carolina 29303

Dear Dr. Hanna:

During an inspection ending on May 16, 1997, Ms. Myla Chapman, an investigator with the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study entitled, "Evaluation of the Safety and Efficacy of[redacted] The inspection is part of FDA's Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of research involving investigational drugs.

Based on our review of the inspection report and information submitted with the report, we identified deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312]. The deviations include, but are not limited to the following:

1. **Failure to ensure that the investigation is conducted according to the investigational plan (protocol). [21 CFR 312.60]**

   Laboratory values were not collected as required by the protocol, one subject was under dosed, and follow-up for subjects was not always carried out per the protocol.

   a. There are no one-day hematology values for subject #020-[redacted]

   b. The FDA investigator reports that there are no one-day laboratory values for subject #010-[redacted]

c. The one-day laboratory values for subject #012 are dated 9/27/95. The baseline lab values are dated 9/18/95. It appears there are no true one-day values for the subject.

d. Subject #001, seventeen years old, received 19.8 of test article. The lowest level dose permitted by the protocol for ages 16 to adults was 20.

e. The case report form (CRF) for subject #006 indicates the subject did not return for follow-up. The CRF also shows that a phone call was placed to the subject over one year following use of the test article to check for adverse events and status. The protocol required follow-up visits at specified intervals.

2. **Failure to maintain adequate records of disposition of the test article. [21 CFR 312.62(a)]**

Drug accountability records are inconsistent and confusing. There are discrepancies between data in the drug accountability records and the CRFs. For example:

a. Drug accountability form dates of use are different than the dates on the (CRFs) for the following subjects:

Subject #	CRF Date	Drug Accountability Date
001	2/17/95	2/10/95
003	3/7/95	3/6/95
005	6/19/95	6/16/95
006	6/20/95	6/19/95
007	6/16/95	6/20/95
016	2/28/96	3/28/95
019	3/25/96	3/29/96

b. Drug record pages dated 2/1/95, 12/13/95, and 10/1/96 show all doses injected as 25 or 25, except for one subject. While the drug record page dated 7/27/95 shows all doses as 1, except for one subject. Drug record pages dated 2/8/96 and 3/25/97 record doses ranging from 0.5 to 3.5.

c. Subject #002 received the correct dosage of 21 according to the CRF, but the drug accountability record shows the subject received 25.

d. Subject #016 received 21 on 2/28/96 according to the CRF, but the drug accountability page dated 7/27/95 lists the subject's date of use as 3/28/95. There is no entry for the amount of drug injected. In addition, the entry on the drug accountability page has a line through it with no initials, date, or changes made regarding the entry. We remind you that proper procedures for correcting records indicate who made changes and when the changes were made.

e. The FDA investigator was unable to accurately tabulate the number of vials of test article that should be currently available for use at the site. Shipment records show [redacted] vials shipped to your site between 1/11/95 and 3/24/97. There are no supporting documents to show the number of vials returned to the sponsor on 11/10/96 or 3/30/97 or the lot numbers involved. The drug accountability record shows that [redacted] vials were returned on 3/30/97.

f. The name of the individual receiving the study drug is the same on drug accountability pages dated 2/1/95 and 7/27/95, but the signatures are obviously different.

These are significant departures from standard recordkeeping practices for investigational drugs. As principal investigator of a clinical trial you are responsible for maintaining adequate and accurate records of the preparation and disposition of the test article.

3. Failure to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21CFR Part 312.60]

There are no consent forms for two subjects, three consent forms were signed after the test article was administered, and one subject signed the wrong consent form as follows:

a. There are no informed consent forms for subjects #005-[redacted] and #004-[redacted]

b. Subject #022-[redacted] signed the wrong consent form. The subject signed a consent form for study [redacted]

c. Subject #012-[redacted] signed the informed consent form on 2/26/96, over four months after the test article [redacted] was performed on 9/19/95.

d. The parent of subject #014-[redacted] signed the informed consent form on 10/24/95, but the test article [redacted] was performed on 10/18/95, six days prior.

e. Subject #015-[redacted] signed informed consent on 12/7/95, but the test article [redacted] was performed on 12/6/95.

In addition, the consent forms for subjects #003-[redacted] and #024-[redacted] show that the subjects did not date the consent forms. The consent form for subject #024-[redacted] also shows that the witness did not date the consent form.

4. **Failure to prepare and maintain adequate and accurate case histories. [21 CFR 312.62(b)]**

There are significant discrepancies regarding the number of subjects in the study at your site. There are deficiencies and discrepancies regarding the documentation of data. For example:

a. Based on our review, your records are not clear as to the number of subjects enrolled in the study. According to your Drug Accountability Records, the site enrolled[redacted] subjects through date of use 7/3/96 for subject #24-[redacted]. The sponsor reported[redacted] subjects to CBER. See part (A) of the Attachment to this letter for specific points.

b. There are discrepancies noted with regard to the Patient Entrance or Exclusion Record. See part (B) of the Attachment to this letter for specific points.

c. There are no source documents to verify lab values for two subjects. There are no values for any subject regarding one test. There is no test article[redacted] report in one subject's file. For example:

i. There are no source documents to verify baseline lab data for subject #022-[redacted] in the CRF dated 5/24/96. These values were collected at[redacted] before the subject was transferred to the Spartanburg Regional Medical Center.

ii. The FDA investigator reports there are no source documents to verify the original one-day lab values on the CRF dated 7/19/95 or baseline lab data for subject #009-[redacted]. In addition, the original one-day lab values and date were changed to match data from a[redacted] report dated 7/12/95.

iii. The FDA investigator reports that there are no[redacted] titer data/documents in any subject folders for the study.

iv. The FDA investigator reports that there is no report for the test article[redacted] in the file for subject #010-[redacted].

5. **Failure to ensure that an institutional review board (IRB) that complies with the requirements of 21 CFR 56 is responsible for the initial and continuing review and approval of the proposed clinical study. [21 CFR 312.66]**

The FDA investigator reports that there are no records of IRB approval for continuation of the study past October 1996. Instead, a renewal for a[redacted] study by the[redacted] sponsor was found in the study binder.

By signing the Statement of Investigator (Form 1572), you agreed to follow FDA regulations while conducting human clinical trials. The commitment includes ensuring that you will conduct the study in accordance with the protocol, that the requirements relating to obtaining informed consent and IRB review are met, and that adequate and accurate records of the study are maintained. Inspection results indicate that you did not follow the protocol, you did not obtain informed consent for some subjects according to federal regulations, you did not maintain complete and accurate records, you did not ensure adequate oversight of study personnel regarding recordkeeping requirements, and you did not ensure IRB review of the study beyond October 1996.

You are currently participating in [redacted]. Continued non-compliance with the regulations governing the use of investigational drugs could affect not only the acceptability of the trial data but also the safety of the human subjects of research.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. Failure to achieve prompt correction may result in enforcement action without further notice. These actions include clinical investigator disqualification which determines a clinical investigator ineligible to receive investigational drugs.

Should you have any questions or comments about the contents of this letter or any aspects of clinical testing of investigational drugs, you may contact Debra Bower, Consumer Safety Officer, Bioresearch Monitoring, Division of Inspections and Surveillance, at (301)827-6221.

Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852-1448, Attention: James C. Simmons, HFM-600.

Sincerely,

for James C. Simmons
Director
Office of Compliance
Center for Biologics and Evaluation
and Research

Enclosures

FDA Form 483, List of Inspectional Observations
21 CFR Part 312
FDA Information Sheets for Institutional Review Boards and Clinical Investigators (includes 21 CFR Parts 50 and 56)

cc:

Philip A. Riedel, M.D., Chairman
Institutional Review Board
Spartanburg Regional Medical Center
101 East Wood Street
Spartanburg, South Carolina 29303

ATTACHMENT

A. Refer to item 4 (a) in the letter and explain the following regarding the drug accountability record:

1. How many subjects were enrolled in the study until 7/3/96? How many subjects withdrew or refused treatment with the test article until 7/3/96? How many subjects were enrolled after 7/3/96? Please provide a complete and accurate accounting of all of the subjects enrolled in the study whether or not each received the test article. We will compare your accounting with documentation collected during the inspection. If subjects are omitted, please explain why.

2. Why are there two subjects designated subject #16 [redacted] and subject #16 -1 [redacted] in the drug accountability record?

3. Why is the entry of subject #16-1 with date of use shown as 12/1/95 listed prior to subject #16 with date of use shown as 3/28/95?

4. Why was subject #16-1 not included in the subjects reported to CBER who received study drug prior to 8/1/96?

5. Why are there two subjects designated as #15, one with initials [redacted] and the other with initials [redacted]?

6. Why is there no subject designated as #18 on the list?

7. Explain why subject [redacted] has no subject number but has a date of use shown as 2/28/96 and refused treatment.

8. What happened to the reconstituted vials of study drug for those who refused treatment, subjects #15? [redacted], no number [redacted] and 21 [redacted]?

9. Why are there no subject's initials listed for subject #26? Instead, the date of use, 8/19/96, is listed in the column for subject's initials.

10. Explain why your signature and date do not appear at the bottom of the drug accountability pages.

B. There are discrepancies and missing data regarding the Patient Entrance or Exclusion Record signed by you. Refer to item 4 (b) in the letter and explain the following:

1. The record does not appear to be prepared in sequential order. Please explain why subject #18-[redacted] is shown on the list prior to subject #15-[redacted].

2. There is no listing of subject[redacted] who refused use on 2-28-96 as shown in the Drug Accountability Record. Please explain.

3. There is no identification number or month/day/year of entrance into the study listed for subject #21[redacted]who refused treatment. Please explain.

4. Please explain why subject #29-[redacted] is deleted from the list. Note: There are no initials or date of the person who deleted the information.

5. Please explain why subject #7 has an entrance date prior to subject #5, why subject #18 has an entry date prior to #14, why subject #16-1 has an entrance date prior to #15, why #17, 19, and 20 have entrance dates prior to subject #16-[redacted], why subject #23 has an entrance date prior to subject #22.

6. Please explain why the form shows that subject #001-[redacted]entered the study on 2/10/95 when the operative report summary states the subject was admitted two days prior to surgery which occurred on 2/19/97.

7. Please explain why subjects #5, 6, and 7 do not directly match subjects #5, 6, and 7 on the Drug Accountability Record.